

**A STUDY OF BASAL THYROID FUNCTIONS IN
DRUG NAIVE FIRST EPISODE DEPRSSION**

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled “**A STUDY OF BASAL THYROID FUNCTIONS IN DRUG NAIVE FIRST EPISODE DEPRSSION**”, is a bonafide record work done by **Dr. KAVITHA. C** under my direct supervision and guidance, submitted to the Tamil Nadu Dr.M.G.R Medical University regulation for **M.D Branch XVIII – Psychiatry**.

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DECLARATION

I, **Dr. KAVITHA. C** solemnly declare that the dissertation titled “**A STUDY OF BASAL THYROID FUNCTIONS IN DRUG NAIVE FIRST EPISODE DEPRSSION**” has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.D degree **Branch – XVIII (Psychiatry)** to be held in April 2012.

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INTRODUCTION

In patients with endocrine disorders there is a high prevalence of mood disorders in general and particularly major depression. Specifically regarding thyroid diseases, according to Boswell et al.,(1997), the prevalence of depressive symptoms is quite higher ranging from (30–50%) where as in patients primarily diagnosed with major depression, there is rarely a picture of overt thyroid dysfunction.

Although, a relationship between clinical disorders of the thyroid gland and depression has been well established, the significance of the association between thyroid function and major depression is much less clear. Hence the possibility of a relationship between thyroid gland, brain and depression has been of interest to both clinicians and researchers for more than two centuries.

According to Joffe et al.,(1990), the reviews on various studies have yielded a conflicting data in thyroid functioning in acute depression, however the most consistent findings have been elevated total thyroxin(T4) or free thyroxin(FT4) within “the euthyroid range” that decreases with treatment for depression.

In India, very little work has been done in this field. Chopra VK et al.,(2001) has done a study on basal thyroid function in depressive illness and concluded that total thyroxin(T4) levels were elevated in the drug naïve first episode depressive patients as compared to health controls. This is in agreement with most of the earlier studies (Whybrow et al., 1972; Takahashi et al., 1974; Kierkegaard and Faber, 1981; Muller and Boning, 1988).

Scope of the Study :

Even though a lot of studies were done in this field World wide, In south India the studies are limited and also there are conflicting datas on thyroid function in acute depression. Hence there is an utmost need to evaluate the basal thyroid function in major depression. So the present study was conducted to evaluate the basal thyroid functions in drug naïve patients with first episode of depression and to compare the findings with the normal controls.

REVIEW OF LITERATURE

I. Thyroid gland:

i) Anatomy: Thyroid is an endocrine gland, situated in the lower part of the front and sides of the neck. The gland consists of right and left lobes that are connected by the isthmus.

The gland consists of numerous acini or follicles about 200 microns in diameter. Each follicle is lined by cuboidal epithelium, whose height varies with the degree of glandular activity. Each follicle contains colloid which normally comprises iodinated 'thyroglobulin'. Between the follicles are 'para follicular cells' also called as 'C-cells'. Follicular cells produces T₃, T₄ and reverse T₃. Para follicular cells produces calcitonin.

ii) Physiological aspects of thyroid hormone:

Thyroid hormones T₄, T₃ and reverse T₃ are synthesized by the iodination of tyrosine residues of thyroglobulin and are stored in the thyroid follicles. The thyroglobulin molecule is a glycoprotein synthesized by the thyroid cells. Thyroxine (T₄) is tetraiodothyronine, while T₃ is triiodothyronine.

SYNTHESIS, STORAGE AND RELEASE OF THYROID HORMONES:

1. IODIDE UPTAKE: Thyroid cells trap iodide from blood by an active transport process, stimulated by the thyroid stimulating hormone (TSH) of the anterior pituitary gland.

2. OXIDATION AND IODINATION: Iodide trapped by the follicular cells is oxidized by peroxidase enzyme to form iodine which combines with tyrosine residues of thyroglobulin to form moniodotyrosine (MIT) and diiodotyrosine (DIT).

3. COUPLING: Pairs of iodinated tyrosine residues couple together to form T₄, T₃ and reverse T₃ by an oxidative reaction.

4. STORAGE AND RELEASE: The thyroglobulin containing iodinated tyrosine residues, remains stored as colloid in the follicles. When the gland becomes active, colloid is taken back into the follicular cells and releases T₃, T₄ and reverse T₃ into the circulation.

5. PERIPHERAL CONVERSION OF T₄ TO T₃: Peripheral tissues like liver, kidney and muscle convert T₄ into T₃ by mono deiodination. About 85 % of T₃ is produced by this way. Although the circulating levels of T₃

are much lower than the T4 levels, T3 is the metabolically active hormone. However T4 is the main determinant of the thyroid hormone available to the brain, T4 crosses the blood brain barrier and converted to T3 within their own cells.

TRANSPORT OF THYROID HORMONES: Within the plasma T3 and T4 are transported bound to plasma protein thyroxine –binding globulin (TBG), so that only 0.3% of T3 and 0.02 % of T4 are free.

REGULATION OF THYROID HORMONE SECRETION:

Thyroid stimulating hormone (TSH) produced by the anterior pituitary gland regulates the synthesis and release of thyroid hormones. It is in turn stimulated by thyrotropin releasing hormone (TRH) produced in the hypothalamus and inhibited by high blood levels of thyroid hormones T3 and T4. TSH secretion has a circadian rhythm with an increase near to midnight (between 10 PM and 4 AM).

iii) BIOLOGICAL EFFECTS OF THYROID HORMONE:

a. METABOLIC ACTIONS:

- 1. EFFECT OF PROTEIN METABOLISM:** The overall effect of T4 is catabolic, that is increased amount of protein being used as energy,

so prolonged action results in negative nitrogen balance and tissue wasting.

2. **EFFECT ON CARBOHYDRATE METABOLISM:** The net effect on carbohydrate metabolism is increase in blood sugar, the thyroid hormones are antagonistic to insulin.

3. **EFFECT ON LIPID METABOLISM:** T4 and T3 enhance lipolysis and at the same time also stimulates lipogenesis. It accelerates all phases of cholesterol metabolism, but its conversion to bile acids dominates.

b. **GROWTH AND DEVELOPMENT:** T3 and T4 are essential for normal growth and development, so their congenital deficiency results in cretinism. Thyroid hormones are essential for axonal and dendritic ramification, synapse formation and myelination.

c. **CALORIGENESIS:** T3 and T4 increases basal metabolic rate (BMR) by stimulation of cellular metabolism.

d. **NERVOUS SYSTEM:** T3 and T4 have profound functional effect on CNS. Mental retardation occurs in cretinism. Sluggishness and other behavioral features occurs in myxoedema. Hyperthyroid individuals are anxious, exhibit tremors and hyperreflexia.

Peripheral Nervous system: The reaction time of “stretch reflexes” is shortened in hyper thyroid and prolonged in hypothyroidism.

II. DISORDERS OF THYROID FUNCTION:

Thyroid dysfunction can be evaluated by thyroid function tests.

1. TSH test:

A high TSH level indicates that the thyroid gland is failing because of a problem that is directly affecting the thyroid (primary hypothyroidism).

A low TSH level indicates that the thyroid is overactive producing excess thyroid hormone (hyperthyroidism).

Occasionally a low TSH may result from an abnormality in the pituitary gland, which prevent it from making enough TSH to stimulate thyroid gland (secondary hypothyroidism).

In most healthy individuals, a normal TSH value means that the thyroid is functioning normally.

Normal TSH level: 0.3 to 4.7 mIU/L.

2. T4 (thyroxine test): T4 circulates in the blood in two forms:

- i. T4 bound to proteins that prevent T4 from entering various tissues that need thyroid hormone.

ii. Free T4 enter the various target tissues to exert its effect.

The free T4 fraction is the most important test to assess thyroid function and tests to measure this is called free T4 (FT4) and Free T4 index (FT4I).

A low TSH with an elevated FT4 or FTI is found in hyperthyroidism.

A low TSH with low FT4 or FTI indicates hypothyroidism due to problem involving the pituitary gland.

A high TSH with low FT4 or FTI indicates primary hypothyroidism due to disease in thyroid gland.

Normal serum thyroxine : 4.6 – 12 $\mu\text{g/dl}$.

Free thyroxine FT4 : 0.7 – 1.9 $\mu\text{g/dl}$

Free T4 index FT4I : 4.6 – 12.

3. **T3 (Triiodothyronine) test:** T3 are often useful for diagnosis of hyperthyroidism or determine the severity of the hyperthyroidism.

A low TSH level with high T3 levels occurs in hyperthyroidism.

A high TSH level with low T3 levels occurs in hypothyroidism.

However T3 testing is rarely helpful in hypothyroid patients, as it is the last test to become abnormal.

Normal Serum Triiodothyronine T3: 80 – 180ng/dl.

FreeT3 index FT3I:80-180.

INTERPRETATION OF RESULTS

TSH	T4	T3	INTERPRET ATION
High	Low	Low or Normal	Hypothyroidism
Low	High or Normal	High or Normal	Hyperthyroidism
Low	Low or Normal	Low or Normal	Pitutary (secondary hypothyroidism)
High	Normal	Normal	Sub clinical Hypothyroidism.

4. **TRH stimulation test (Thyrotropin Releasing Hormone):** It is sometimes used in the workup of the thyroid function. The procedure involves intra venous (IV) injection of 500 mg of TRH, which produces a sharp rise in serum TSH when measured at 15, 30, 60 and

90 minutes. A normal response is a rise in TSH of 5 microu/ml or more above the base line level. In hypothyroid patients, the response is exaggerated, whereas in hyperthyroid patients it is blunted. Its use as a diagnostic tool in the psychiatric assessment of depression has waned as its specificity and sensitivity are poor. For example, although some patients with depression experience elevation of TSH often following TRH infusion, others have a blunted response.

5. THYROID ANTIBODY TEST: In many patients with hypothyroidism or hyperthyroidism, lymphocytes makes antibodies against thyroid that stimulate or damage the gland. Two common antibodies that cause thyroid problems are against thyroid peroxidase and thyroglobulin. Measuring of thyroid antibodies may help diagnose the cause of thyroid problems.

Thyroid peroxidase antibody or Anti microsomal antibody (TPO Ab):
This antibody is present in Grave's disease, Hashimoto's thyroiditis.

Thyroglobulin antibody (TgAb): This antibody is present in thyroid cancer, Hashimoto's thyroiditis.

TSH Receptor antibody: This antibody is present in Grave's disease.

III.NEUROPSYCHIATRIC ASPECTS OF THYROID DYSFUNCTION:

Disorders of thyroid gland falls into two general categories:

Hyperthyroidism or Hypothyroidism

A) Hypothyroidism:

It results from inadequate synthesis of thyroid hormone and is categorized as overt or subclinical.

Overt (Grade 1) Hypothyroidism : These patients have classical signs and symptoms of hypothyroidism. Lab values show decreased T4 and elevated TSH and increased TSH response to TRH.

Subclinical Hypothyroidism (SCHT) : These patients are by definition, asymptomatic with normal thyroid hormone levels but elevated TSH. They are graded as follows: (Gold et al.,1981)

Grade 2 Hypothyroidism: These patients have normal T3 and T4 but elevated TSH and increased TSH response to TRH.

Grade 3 Hypothyroidism: These patients have normal T3 and T4 and TSH, but increased TSH response to TRH.

The most common cause of hypothyroidism in adults is Hashimoto's thyroiditis. Other causes of hypothyroidism includes idiopathic atrophy, endemic hypothyroidism from deficiency of dietary iodine, hypopituitarism (from post partum pituitary neurosis), hypothalamic disease resulting from deficient production of TRH and iatrogenic hypothyroidism (caused by drugs such as Lithium or Anti thyroid drugs or from surgical or chemical thyroidectomy).

Epidemiology: The prevalence of overt hypothyroidism is approximately 2% in women and less than 0.1 percent in men. SCHT predominates in women, occurring in approximately 7.5% of women and 3% in men. Women appear to have higher rates of hypothyroidism because of their greater rates of auto immune disease. As the prevalence of auto immune disease rises with age, the prevalence of overt and SCHT also rises with age, particularly in women.

Physical features: Signs and symptoms includes cold intolerance, constipation, paresthesias, muscle cramps, menstrual disturbances (amenorrhea or menorrhagia), reduced hearing, weight gain, brittle and thin hair, husky voice, slowed deep tendon reflexes (DTR), bradycardia, cardiomegaly, low voltage complexes on ECG, elevated levels of cholesterol and triglycerides and normochromic and normocytic anemia.

Neuropsychiatric features:

Cognitive disturbances: includes the inability to concentrate, poor attention, bradyphrenia, calculation difficulties and difficulty understanding complex questions and memory impairment.

Depressive syndrome: Depressive affect has been reported as a frequent association with hypothyroidism Whybrow et al.,(1969). Several of the metabolic and behavioral changes seen in hypothyroidism are common to depression, suggesting the changes in the pituitary-thyroid axis system may play a role in the modulation of mood.

The most common abnormality in thyroid function testing among patients with depression is a mild elevation in serum thyroxine concentration, which falls with clinical response to treatment (Whybrow and Bauer 2000).

Serum TSH response to thyrotropin- releasing hormone is blunted in 25% of depressed patients and nocturnal surge of TSH is lost in depression, returning to normal with recovery (Whybrow and Bauer 2000).

Psychosis: A psychotic syndrome of auditory hallucinations and paranoia named myxedema madness, has been described in some patients.

SCHT: may produce depressive symptoms and cognitive deficits, although these tend to be less severe than those produced by overt hypothyroidism. Among patients with SCHT, the lifetime prevalence of depression in patients is approximately double that of the general population. A lower response rate to antidepressants has been observed among patients with SCHT, in addition to greater likelihood to respond to T3 augmentation as compared to euthyroid depressed patients.

B. Hyperthyroidism: Hyperthyroidism or thyrotoxicosis results from over production of thyroid hormones by the thyroid gland. The most common cause is Graves disease. Toxic nodular goiter causes another 10% of cases among middle aged and elderly patients. Other causes include hyper functioning solitary thyroid adenomas, thyroiditis, use of exogenous thyroid hormones, TSH- producing pituitary adenomas, pituitary resistance of suppression of TSH, secretion by the thyroid hormone, thyroid carcinoma, choriocarcinoma, hydatiform moles and struma ovarii.

Thyroid storm (thyrotoxic crisis) is a life threatening syndrome that is usually precipitated by illness or injury but also develops after withdrawal from anti thyroid drugs or often therapy with RAI (Radio active Iodine). Symptoms include marked tachycardia, weakness, fever and altered mental status.

Epidemiology: In the general population, the presence of hyperthyroidism is approximately 0.5%. Graves disease is the most common cause, accounting for 80% of cases. Graves disease occurs four times more frequently in women than men. The prevalence of thyroiditis is estimated to occur in 5 to 9 % of women in the post partum period, usually resolving spontaneously by one year after delivery.

Physical features: Signs and symptoms of hyperthyroidism include increased pulse rate, arrhythmias, elevated blood pressure, fine tremor, heat intolerance, excessive sweating, increased appetite, weight loss, palpitation, tachycardia, menstrual irregularities, muscle weakness, exophthalmos, lid lag, hyper active deep tendon reflexes.

Cognitive symptoms: It includes a short attention span, impaired recent memory and exaggerated startle response.

Psychiatric features : it includes nervousness, fatigue, insomnia, mood liability and dysphoria.

In several cases, there may be visual hallucinations, paranoid ideation and delirium. Although some symptoms of hyperthyroidism resembles that of a manic episode, an association between hyperthyroidism and mania has rarely been observed.

C. POST PARTUM THYROIDITIS:

Post partum thyroiditis is a common thyroid disorder that presents during the first post partum year. It is the occurrence of either transient hyperthyroidism, transient hypothyroidism, or transient hyperthyroidism followed by transient hypothyroidism.

Etiology: Post partum thyroiditis is an exacerbation of an underlying autoimmune thyroiditis, aggravated by the immunological rebound that follows the partial immunosuppression of pregnancy. Prevalence of post partum thyroiditis ranges between 1.15 and 16.7% with a mean prevalence of 7.2%.

Clinical features: Symptoms can occur during either phase of post partum thyroiditis.

The hyperthyroid phase presents with palpitation, fatigue, heat intolerance, irritability and nervousness. This phase is diagnosed by the combination of low serum TSH concentration in the presence of thyroid peroxidase antibodies. In women who are TSH receptor antibody- negative, free T4 levels are typically elevated but may be normal.

The hypothyroid phase of thyroiditis presents with impaired concentration, poor memory, decreased energy and dry skin. An elevated

TSH in the presence of antithyroid peroxidase antibody is pathognomic for post partum thyroiditis.

Post partum depression: Studies evaluating the association between post partum thyroiditis and post partum depression have yielded varying results. Investigations have evaluated both the impact of hypothyroidism and the presence of thyroid antibodies (antithyroid peroxidase and for antithyroglobulin) on the development of post partum depression. Two studies by Hayslip CC., et al 1988 & PopVJM., et al 1991 reported an association between hypothyroidism and post partum depression, whereas two other study reports by Harris B., et al 1992 & Kujipens., et al 2001 discovered an increased rate of depression in euthyroid women ,who were thyroid antibody positive during post partum. One study by Kent GN ., et al 1999 found no correlation.

IV. DEPRESSION AND THYROID DYSFUNCTION

1. DEPRESSION AND THE HYPOTHALAMUS-PITUTARY-THYROID AXIS:

The link between mood disorders and abnormalities of the HPT axis can be studied by the assessment of functional thyroid tests in patients with primary mood disorder. It has been argued that depression might be characterized by a 'low-thyroid function syndrome' (Legros et al. 1985;

Staner et al. 1992; Rao et al. 1996). Hypothyroidism is associated with refractory depression, suggesting that this characterizes one biological subtype of refractory depression.

Screening thyroid tests are often routine for depressed inpatients, but data suggest that thyroid screening may add little to the diagnostic evaluation. Overt thyroid disease is rare among depressed inpatients (Ordas and Labbate 1995), and the role of thyroid hormones in the pathophysiology of affective disorders remain to be clarified (Joffe and Sokolov 1994).

A) **T4 (Thyroxine)** : According to (Jackson., et al 1999) he concluded that most patients with depression, although generally viewed as chemically euthyroid, have alteration in their thyroid function. It includes

1. Slight elevation of serum thyroxine (i.e within the normal range)
2. Blunted thyrotropin response to TRH stimulation
3. Loss of nocturnal TSH rise.

These changes were generally reversed following alleviation of the depression. He postulated that hypercortisolism of depression (which occurs due to impaired functioning of the hippocampus, which is the negative feed back site of glucocorticoids, along the hypothalamic hypophyseal adrenal axis) lead to an activation of the hypothalamic neurons which produces

TRH and consequently the increase of T4. The increased TRH secretion may lead to down regulation of the TRH receptor leading to blunted TSH response to TRH stimulation.

According to Bauer and Whybrow 1988, in some cases of depression the brain would be TH deficient and the relative increase of thyroxine would exert a compensatory role in the maintenance of the “affective homeostasis”, offering more T4 for the brain with deficiency of this hormone, seeking to normalize function.

A review by Musselman., et al 1998 concerning the HPT axis, depressed patients have been reported to have:

1. Alteration in the thyroid stimulating hormone response to thyrotropin-releasing hormone (TRH)
2. An abnormally high rate of antithyroid antibodies; and
3. Elevated cerebrospinal (CSF) TRH concentrations.

Hence with regard to T4 most of the studies of major depressive disorder have found an relative increase (i.e within the normal range) of iodothyronines, mostly notably hyperthyroxinemia (i.e serum FT4, total T4). Neuro biologically, this thyroid activation has been proposed to represent a compensatory mechanism to a pathological process, that is depression or the primary pathology itself.

B. T3 (Triiodothyronine):

With regard to Triiodothyronine (T3) Kirkegaard and Faber et al., (1986) have found no alterations in the free T3 serum levels in depressed patients. In one study by Kirkegaard et al., (1990) the daily production of T3 among non medicated and moderately depressed subjects was within the normality. It raises the hypothesis that the combination of the production of increased T4 with the production of normal T3 suggest a conversion of T4 into reduced T3 caused by the reduction in the enzymatic activity of deiodination, probably in the brain.

It has been proposed by (Nemeroff., et al 1989) that in depression there is an inhibition of the 5'-deiodinase type II (D-II) enzyme, probably due to the increase in cortisol levels. This enzyme is responsible for the transformation of T4 into active T3 in the brain, consequently its inhibition triggers the conversion of T4 by type III brain 5'-deiodinase (D-III) , producing reverse T3 (rT3). A defect in brain deiodinase can be a pathogenic factor in depression, raising the possibility of central or brain hypothyroidism.

C.TSH : with regard to thyrotrophin (TSH) Cleare et al., (1996) found a positive relation between depressive scores and the increase in TSH levels, confirming the previous findings of this same group. A probable hypothesis for the increase in serum TSH in depression stems from the observation that

the plasma level of this hormone is influenced by somatostatin, which inhibits TSH release from the hypophysis. In some studies (Rubinow DR et al., 1983 & Bissette G et al., 1986), they found a reduction in somatostatin in the CSF of depressed subjects, which may contribute for the increase of serum TSH in depressive conditions.

Although plasma TSH levels in depressed patients are not conclusive, A Study by (Bartalena et al., 1990) concluded that endogenous major depression is associated with an important impairment in the nocturnal secretion of TSH, being a more sensitive alteration of the HPT axis in endogenous depression than the TRH challenge test.

This nocturnal reduction in TSH can lead to global decrease in the secretion of thyroid hormone, enabling a certain degree of central hypothyroidism in some depressed patients.

D. Response of TSH to TRH: Prange., et al. (1972) in patients with major depression, observed the presence of decreased response of TSH to TRH stimulation in 25 % of these cases and all these patients had normal TSH, T3 and T4 plasma levels. Still in the same year Kastin AJ et al., (1972) confirmed those data, afterwards reconfirmed by other studies which defined this decreased TSH response to TRH as the most widely recognized evidence of thyroid axis abnormality in depression. This decrease or blunted response to TSH occurs in 25 to 30 % of depressive individuals.

On the other hand, there are studies with depressed patients which found an increased TSH response to TRH (Extein I et al.,(1982) & Gold MS et al.,(1981).It is calculated that nearly 10 to 17 % of depressed individuals showed an exaggerated response to the test (Nemeroff CB.1989 & Gold MS et al.,1981). These cases use to have normal TSH, T3, T4 plasma levels, the so called ‘grade III hypothyroidism’. In 1982, Gold., et al found 60 % of cases with positive anti thyroid antibodies among depressed patients with exaggerated response to TRH, being the first report that some depressive pictures show high rates of asymptomatic auto immune thyroiditis.

Recently Kraus et al.,(199 7) investigated 60 depressed patients and concluded that mild alteration in thyroid function may contribute for depression in some cases and utilization of the TRH challenge test as the most sensitive one to investigate the thyroid alterations which could contribute to the depressive picture and / or hamper their recovery.

E. Thyrotropin-releasing hormone(TRH):

Banki et al .,(1988) assessed brain TRH among depressive and manic pictures and among controls. Depressed patients showed an increase in TRH levels nearly three fold than controls. This chronic stimulation of TRH in the hypophysis could be responsible for the TSH and T4 serum alterations found in depressed patients.

Blood Brain Barrier and TH transportation:

Transthyretin (TTR): It is one of the T4 serum transporting protein. Only one study has investigated this protein in depressive disorders, and have found significantly decreased levels of TTR among patients with refractory major depression as compared to the control group, and the authors have suggested that the low levels of this transporting protein may cause ‘brain hypothyroidism’, accompanied by peripheral concentration of thyroid hormones within the normal range (Hatterer JA., et al.1993). With the lower availability of thyroid hormones in the brain, there is an increase in the hypothalamus production of TRH, resulting in increased values of TRH in the CSF and an decreased response of TSH to TRH. The authors suggest that a thyroid dysfunction may represent a pathophysiological phenomenon in a sub group of depressed patients.

2. TYPES OF DEPRESSION AND THYROID DYSFUNCTION

a. **POST PARTUM DEPRESSION:** The most robust relationship between thyroid dysfunction and depression is in the post partum period. They found that women who have underlying sub clinical auto immune disease may get exacerbation following delivery, leading to the production of thyroid antibodies which may cause thyroid dysfunction either overt or latent hypothyroidism leading to depression. However again the literature is split and the results are inconclusive.

b. ENDOGENOUS DEPRESSION: A study by Bartalena et al., (1990). noted that patients with endogenous major depression had an impairment in the nocturnal secretion of TSH which is a sensitive alteration in the HPT axis. This nocturnal reduction in TSH can lead to global decrease in the secretion of thyroid hormone, enabling a certain degree of central hypothyroidism in these patients.

c. SEVERE DEPRESSION WITH PSYCHOTIC FEATURES: A study by Vinod kumar., et al. 2001 found there was no significant difference between depressive patients with and without the presence of psychotic features and with and without the presence of somatic syndrome with respect to total T3 and total T4. However depressive patients with psychotic features had significantly higher mean value of thyroid stimulating hormone (TSH) as compared to those without psychotic features.

Joffe., et al 1992 did not find any difference between patients with melancholic and non melancholic depression with respect to total thyroxine T4, total triiodothyronine T3 and thyroid stimulating hormone TSH. Joffe and Levitt 1990 found significantly lower total triiodothyronine T3 and significantly higher thyroid stimulating hormone TSH in patients with psychotic depression compared to non psychotic depression.

An exploratory study on thyroid function in clinical subtypes of major depression was done by Fountaulakis et al.,(2004) he concluded that no significant differences can be traced concerning the thyroid function between clinical subtypes of depression nor there is any correlation between specific clinical symptoms and thyroid indices.

3. DEPRESSION AND THE AUTO IMMUNE HYPOTHESIS:

The hypothalamus-pituitary-thyroid axis (HPT) is not isolated from the rest of the endocrine system, and it is heavily influenced by auto immune disorders and stress.

Any significant changes in the stress system activity, such as acute or chronic stress or even cessation of chronic stress, severe exercise, pregnancy, the post partum period, anxiety and mood disorders may suppress or potentiate auto immune disease activity and/or progression through modulation of the systemic or local pro/ anti inflammatory cytokine balance (Elenkov and Chrousos.2002).

Musselman and Nemeroff (1996), reported that depressed patients had an abnormally high rate of anti thyroid antibodies. Gold et al., (1982) found that auto immune thyroiditis was found in 15 % of depressed patients with exaggerated response to the TRH stimulation test.

The finding that depression often co-exists with auto immune subclinical thyroiditis suggests that depression may cause alterations in the immune system, or that in fact it could be an auto immune disorder itself.

It is also believed (although not well documented) that depression is accompanied by various direct and indirect indicators of a moderate activation of the inflammatory response system. Increased production of proinflammatory cytokines, such as Interleukin-1, Interleukin-6 and Interferon (IFN- γ) may play a crucial role in the immune and acute phase response in depression (Van west and Maes.1999).

How ever, the research in the area of psycho immunology is very delicate and one should be very careful in interpreting results. Apart from problems arising from the limitations in laboratory techniques themselves, depressed patients may suffer from secondary alterations of immune function, while controls may be 'super-normal'.

4. RELATIONSHIP BETWEEN ALTERATIONS OF THE HYPOTHALAMUS-PITUTARY-THYROID (HPT) AXIS AND SEROTONIN.

Evidence that serotonin, a neurotransmitter strongly involved in depressive states, also has a pathophysiological role in thyroid disease stems from several observations. Research by Cleare et al., (1996) have noticed

that the hypothyroidism reduces central (5-HT) activity in the brain. They found a positive relationship between depressive scores and the increase in the TSH levels. They also suggest a threshold effect in that higher TSH levels predicted lower 5HT mediated endocrine responses and the presence of clinical depression. This same group of researchers, in a further investigations on the serotonergic function in patients with hypothyroidism, have confirmed the previous findings and noticed that the serotonergic function was normalized by replacement therapy with thyroid hormones.

Evidence for interaction of serotonin with thyroid hormone. Stems from following observation:

1. The use of T3 can reduce the activity of the 5HT_{1A} auto receptors and then increase the cortical release of 5HT.(AltshulerLL et al.,2001)
2. Both in hypothyroidism and hyperthyroidism the functioning of thyroid hormone metabolizing enzymes can affect the brain levels of serotonin.
3. Depression causes an inhibition of type II deiodinase enzyme leading to a decrease in the brain levels of T3 and contributing to the decrease of serotonin in depressive pictures (Nemeroff CB. et al., 1989).

Kirkegaard and Faber et al., 1998 believe that serotonin deficiency, a main pathogenic factor in depression is sufficient to explain the alterations in the HPT axis in depressed patients, especially endogenous ones.

5. STRESSFUL LIFE EVENTS & DEPRESSION : Studies have shown that compared to healthy controls depressed patients have significantly greater number of life events prior (6-12 months) to the onset of their illness(Chatterjee RN.et al.,1981,Satija YK et al.,1998, Prakash et al.,1980) .In terms of type of life events, it is seen that depressed patients experience high proportion of life events related to death of family member, personal health related problem, bereavement, inter personal and social events(Chandran M et al.,2002,Chatterjee RN et al .,1981).

It is also seen that compared to patients with mild depression, patient with moderate and severe depression tend to use avoidance as coping strategies more frequently for the stressful life events, suggesting that it may be a maladaptive way to cope with the situation, which is responsible for development of depression (Satija YK et al .,1998).

6. INDIAN STUDIES:

An overview of Indian Research in depression was done by Grover S.et al.2010.

Depression is a disorder of major public health importance in terms of its prevalence, suffering, dysfunction, morbidity and economic burden. The

report on Global burden of Disease estimates the point prevalence of Unipolar depressive episode to be 1.9 % for men and 3.2 % for women. One year prevalence has been estimated to be 5.8 % for men and 9.5 % for women.

Demographic and psychological risk factors for depression:

In terms of socio demographic variables, studies by (Sethi et al.,1979,Poongothai et al.,2009,Nandi DN et al.,1979, Bagadia VN et al., 1973 Ramachandran V et al., 1982) have shown that depression is more common in women, in subjects with low socio economic background (Poongothai et al.,2009, Bagadia VN et al.,1973, Mohandas E et al.,2009) those who are divorced or widow (Poongothai et al.,2009) or those residing in urban areas(Reddy MV et al.,1998) .

THYROID DYSFUNCTION:

Two studies by (Boral GG et al.,1980 and Saxena J et al.,2000)have found that significantly higher number of patients with unipolar depression have subnormal T3 and T4 levels and a corresponding increase in TSH levels compared with healthy controls.

In a second study by Saxena J et al.,2000, mildly depressed patients had significantly lower TSH and severely depressed patients had higher TSH suggesting the direct relationship of severity of depression and TSH levels. Another study Gupta S et al.,2008 found that 20.5% subjects of

major depressive disorders have hypothyroidism. A study by (Chopra VK et al.,2001) on drug naïve first episode depression patients showed significantly higher T4 levels, but there was no significant difference in the level of T3 and TSH between depressed and healthy control subjects.

When depressed subjects with and without psychotic features were compared, it was seen that subjects with psychotic symptoms had significantly higher levels of TSH.

Study by Gautam S. 2010 Hypothyroidism can cause depression, cognitive impairment and rapid cycling mood disorder. Subclinical hypothyroidism also cause an increased frequency of sub syndromic depression.

SYMPTOMATOLOGY: One common theme with regard to symptomology of depression, which has been reported by most of the research, is high prevalence of somatic syndromes and several studies report that somatic symptoms are the most common manifestation of depression in Indian sub population.

Depression is the most common psychiatric disorder reported in most of the community based studies in India. Further studies from India has also shown that life events during the one year period preceeding the onset of depression plays a major role in depression. Studies on women also shows the importance of identifying risk factors like inter personal conflicts and

marital disharmony and focusing on improving social network and psycho education may prevent the development of depression.

There are several papers suggesting that the thyroid function of depressed patient is within the normal range, hypothyroidism and hyperthyroidism are extremely uncommon and that the presence of subtle thyroid function abnormalities does not have an impact on treatment outcome.

(Joffe 1987; Harris et al., 1989; Fava et al., 1995; Joffe et al., 1996; Pop et al., 1998).

However, on the contrary, there are even more papers supporting the idea of a sub clinical thyroid dysfunction, especially in melancholic or refractory patients, possibly of an auto immune origin (Banki et al., 1985; Kjellman et al., 1985; Nemeroff et al., 1985; Gewirtz et al., 1988; Marchesi et al., 1988; Nemeroff 1989; Rao et al., 1989; Rupprecht et al., 1989; Howland 1993; Bunevicius et al., 1994; Maes et al., 1994; Rao et al., 1996) suggesting that subclinical hypothyroidism may lower the threshold for the occurrence of depression (Haggerty et al., 1993) or generally to any mental disorder (O'Donnel et al., 1998; Stein and Uhde 1989; Haggerty et al., 1990).

Thus review of literature suggest that most patients with depression, although generally viewed as chemically euthyroid, may have alterations in their thyroid function (Joffe et al., 1992; Custro et al., 1994; De Mendonca Lima et al., 1996) including slight elevation of the serum FT4 (especially in

melancholic patients) (Mades et al.,1993), blunted TSH response to thyrotropin releasing hormone(TRH) stimulation (Loosen 1985), and loss of nocturnal TSH rise, and this may reflect brain hypothyroidism in the context of systemic euthyroidism (Bauer et al.,1990; Jackson 1998; Sullivan et al.,1999).

AIM AND OBJECTIVES

Aim:

To assess the basal thyroid functions in patients with first episode depression and to compare with controls

Objectives:

1. To assess the level of serum T3, T4, TSH in patients with first episode depression and to compare with that of age & sex matched controls.
2. To correlate the severity of depression and thyroid hormone level.
3. To assess the relationship of socio-demographic profile with thyroid hormone level and severity of depression .
4. Presumptive stressful life events and its impact on severity of depression and its relationship with thyroid hormone levels.

Hypothesis:

1. Serum T4 level is higher in depression compared to controls.
2. Serum TSH level has no significant difference in depression compared to controls.
3. Serum T3 and T4 level is significantly higher in severe depression compared to mild/moderate types.
4. Subclinical hypothyroidism is more common in females than males.
5. Stressful life events increases the severity of depression

MATERIALS AND METHODS

Inclusion Criteria:

1. Age : 25-45years , male & female for both cases and controls.
2. Patients diagnosed as Depressive disorder(according to ICD-10 DCR criteria)who are drug naïve & first episode as cases and controls selected based on those without present / past physical or psychiatry illness.
3. Patient who are cooperative and have given consent

Exclusion Criteria

1. Individuals with past history of psychiatric disorder
2. Individuals with history of any systemic illness/substance abuse or dependence in the past or present
3. Patients & controls on any psychiatric medications
4. Patients who have been already diagnosed as hypothyroid or hyperthyroid or on any thyroid medication.

Methodology:

Sample of 50,of whom 25 are newly diagnosed patients as Depressive episode and who are drug naïve presenting in our OP department and another 25 are controls are screened for thyroid function .Thyroid hormone

level assessed after 12hrs fasting between 8am and 9am.They are assessed for cross sectional study

Standard Tools:

1. Proforma
2. ICD-10 DCR criteria
3. Hamilton rating scale for depression
4. Presumptive stressful life event scale
5. SES scale

To asses the thyroid dysfunction in depression by assessment of basal thyroid hormone level.

Operating design:

1. The study is planned to be conducted between January 2011 to October 2011.
2. Patients and controls who meet the above inclusion and exclusion criteria are chosen from Psychiatric OP and shown to Senior Psychiatrist and on his advice are included in the study
3. Patients and controls are explained about the nature of the study and informed consent are obtained for inclusion in the study.

4. Patients and controls have been assessed based on detailed history obtained from reliable informant. Complete physical and neurological examination done & detailed mental status examination done. Biochemical investigations are being done in accredited lab. Clinical examination done on two sessions on consecutive days.
5. All the above groups have been subjected to the above tools before starting the medication.

Statistical design:

Statistical design was formulated using the data collected as above, for each of the scales and sociodemographic variables the central values and dispersion were calculated. In comparison of the data for categorical variables chi-square and for numerical variables student t test were used

Tools Used :

1. Proforma

Proforma includes personal demographic details, personal history, past history, family history, physical and Mental status examination and biochemical investigations.

2. ICD-10 (DCR) : the diagnostic criteria for research accompanying the ICD-10 (DCR) are designed for use in research ; their content is derived from the Glossary to the chapter on Mental and Behavioural Disorder in the “Clinical Descriptions and Diagnostic Guidelines” (CDDG) that have been produced for general clinical and educational use by psychiatrists and other mental health professionals (WHO 1992).

3. Hamilton Rating Scale for Depression (HAM-D):

The Hamilton Rating Scale for Depression (HAM-D) is one of the most popular depression assessment instruments among the clinician scales in the field of Clinical and Health Psychology. The first version was published by Max Hamilton in 1960. He designed the scale as a measure of the severity of depression in previously diagnosed depressed inpatients (Hamilton, 1960). Since then different versions have been developed. Although people usually use the 17-item version, the original version had

twenty-one items but Hamilton himself decided that the last four items (diurnal variation, depersonalization/derealization, paranoid symptoms, and obsessional and compulsive symptoms) should not be considered part of the disease, because they are not as frequent as the others and therefore should not contribute to the total score. There is another version in which three new items have been added, to make the 24- item version: helplessness, hopelessness, and worthlessness (Paykel, 1985; Rosenthal and Klerman, 1966).

Hamilton depression scale has been the standard for the assessment of depression for more than 40 years. Many of the psychometric properties of the Hamilton depression scale are adequate and consistently meet established criteria. The internal, interrater, and retest reliability estimates for the overall Hamilton depression scale are mostly good, as are the internal reliability estimates at the item level. Similarly, established criteria are met for convergent, discriminant, and predictive validity, although the latter does suffer somewhat due to multidimensionality. At the item level, interrater and retest coefficients are weak for many items, and the internal reliability coefficients indicate that some items are problematic. The lack of individual item reliability is not necessarily a fatal psychometric flaw; what is critical is that the items as a whole provide adequate reliability.

4. PRESUMPTIVE STRESSFULL LIFE EVENT SCALE:

Developed by Gurmeet Singh et al.(1983), it was constructed and standardized for use in the Indian population. It is a standardization of the Social Readjustment Rating Scale (SRRS).It is in the form of an inventory of 51 items, each item having a weighted stress score. For example death of spouse=100; going on pleasure trip=20, conflict over dowry=51.The items are further categorized as personal or impersonal events, desirable or undesirable or ambiguous events. It is administered in the form of a semistructured interview, wherein the events are assessed to be either present or absent.

5. Kuppuswami scale : (Socio-economic Status)

Kuppuswami scale is widely used to measure the socio-economic status of an individual in urban community based on three variables namely education, occupation and income. The modification of Kuppuswami scale meant to determine the socioeconomic status of family based on education and occupation of head of the family and per capita income per month has also been widely used.

Limitations of the Study :

1. Being a cross sectional study with small sample size the findings derived may not reflect universal population.

2. The higher mean (T4) levels noted in depressives significantly decreased with response to various treatments. In this study, the level of thyroxin (T4) were not performed after the recovery and this remains one of its limitations.

3. Further thyroid function tests like TSH response to TRH, CSF analysis of TSH levels, tests to determine nocturnal rise in TSH, thyroid autoantibodies are not done in our study, which would have given more insight about thyroid abnormalities in depressives.

4. From our sample size, since none of the cases had psychosis, the findings of hormonal levels could not be ascertained in patients with psychotic depression.

RESULTS AND INTERPRETATION

Table 1

Table showing Socio demographic profile of cases and controls

Sl.No	Variable	Cases (N=25) n	Controls (N=25) n	P value
1	AGE			0.77
	< 30 years	13	10	
	31 - 40 years	7	12	
	> 40 years	5	3	
2	SEX			1.0
	Male	5	5	
	Female	20	20	
3	MARITAL STATUS			0.5
	Married	22	23	
	Unmarried	3	2	
4	RESIDENCE			0.773
	Rural	16	15	
	Urban	9	10	
5	SES			0.157
	Lower Middle	15	9	
	Upper Middle	10	16	

Table 1 shows the comparison of socio demographic variables between the depressive and the control groups. Majority of patients with depression (80%) were below 40 years and 88 % of controls were below 40 years. 80% of both cases and controls in our samples were females. Majority of depressives (88%) and controls (92%) were married. More than 2/3 of our sample in cases (64%) and controls (60%) belong to rural background. 60 % of depressive were of low socio economic status and 64 % of controls were of middle socio economic status. There was no significant difference between the two groups with respect to age, sex, marital status, socio economic status and residence.

CHART – 1

MEAN AGE

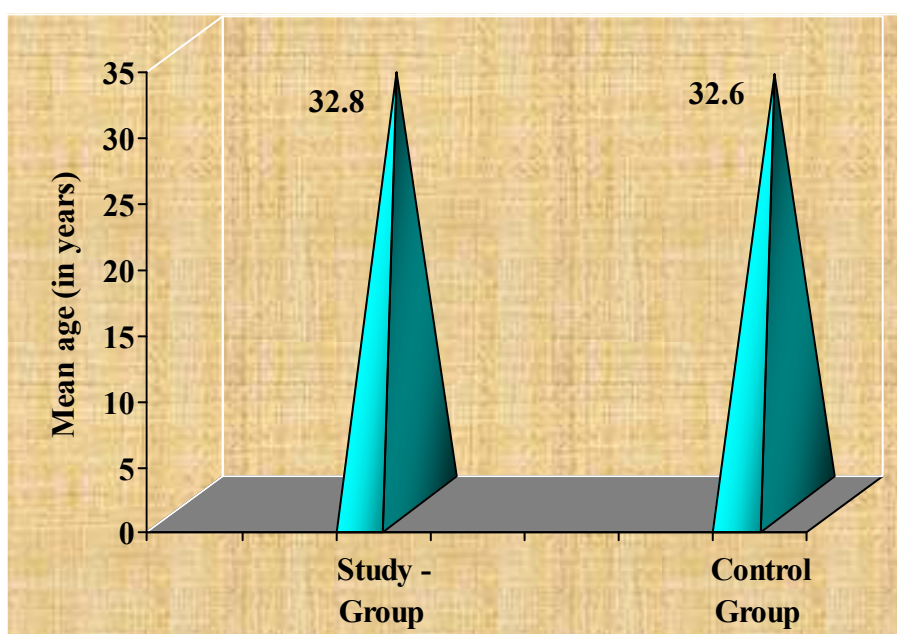


Table 2
Table showing Thyroid Hormone values of cases and controls

Sl.No	Variable	Cases (N=25) n	Controls (N=25) n	P value
1	<u>T3 value</u> <u>(60-200 ng/dl)</u>			0.2855
	≤ 200 ng/dl	25	25	
	≥ 200 ng/dl	0	0	
	Range	75-131	79-141	
	Mean	105.4	102.1	
	SD	15.8	15.6	
2	<u>T4 value</u> <u>(4.5-12 µg/dl)</u>			0.0041*
	≤ 12 µg/dl	22	25	
	≥ 12 µg/dl	3	0	
	Range	6.4-13	5.4-11.1	
	Mean	9.83	8.45	
	SD	1.7	1.25	
3	<u>TSH value</u> <u>(0.3-5.5 mIU/ml)</u>			0.3083
	≥ 5.5	2	0	
	≤ 5.5	23	25	
	Range	0.03-10.59	0.87 - 5.18	
	Mean	2.36	2.27	
	SD	2.32	1.13	

P < 0.05 * P < 0.001**

Table 2 shows the comparison of total thyroxin (T4), total triiodothyronine (T3) and thyroid stimulating hormone (TSH) between the depressive and the control groups. Almost all patients with depression and controls had serum T3 value < 200 ng/dl. Mean T3 value for depressive was 105.4 and for control was 102.1. The mean T3 value of both cases and controls were not significantly different.

Twenty two patients with depression (88 %) had serum T4 value within normal range and three patients had high T4 value. Among controls all had normal value. Mean T4 value for depression was 9.83 and for control was 8.45. The difference was higher in depressive group which was statistically significant.

Two patients with depression had higher TSH values (8 %) and rest of the patients and controls had normal TSH levels. There was no difference between the mean value of thyroid stimulating hormone (TSH) between the two groups.

CHART – 6

MEAN T3

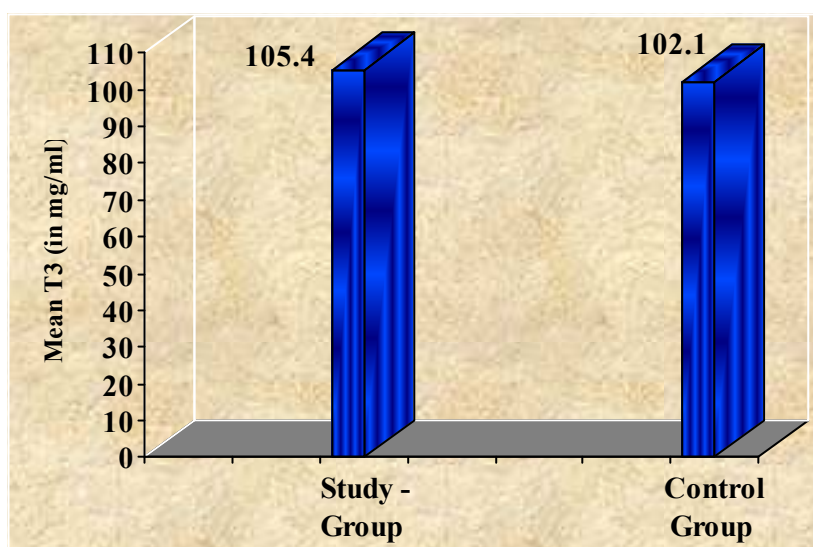


Table 3
Table showing PSLE and PSLE scoring in cases and controls

Sl.No	Variable	Cases (N=25) n	Controls (N=25) n	P value
1	<u>PSLE</u>			0.0001 **
	≤ 2	18	25	
	≥ 2	7	0	
	Range	1-4	0-2	
	Mean SD	2.08 1	0.92 0.7	
2	<u>PSLE score</u>			0.0001 **
	≤ 200	21	25	
	≥ 200	4	0	
	Range	47-247	0-134	
	Mean SD	119 58.3	49.8 40	

[P < 0.05 *, P < 0.001**]

Table 3 shows the presumptive stressful life events in cases and controls. Seven depressive (28 %) had more than two life events in the past one year. The rest of the patients and controls had less than two life events in the past one year. The difference was statistically significant. The trend suggests stressful life events within one year significantly increase the onset of depression.

Four patients with depression (16 %) had presumptive stressful life event score more than 200, rest of the patients and controls had presumptive stressful life event score < 200. The mean PSLE score for depression was 119 and for the control was 49.8 which shows statistically significant difference.

Table 4

Table showing PSLE and Thyroid hormone values in MDD cases

S.No.	Variable	Thyroid hormone values					
1	PSLE	T3		T4		TSH	
		Mean	SD	Mean	SD	Mean	SD
	≤ 200	106.7	15.9	9.95	1.66	2.4	2.48
	>200	98.8	15	9.23	2	2.11	1.42
	'p' value	0.2496		0.4143		0.9704	

Table 4 : Shows the relationship between presumptive stressful life events and the thyroid function values in depressives. The mean serum T3 levels in patients with depression with life event score < 200 was 106.7 and more than 200 was 98.8 showing no statistical difference. On comparison of patients with less than 200 and more than 200 in presumptive stressful life event score in relation to serum T4 levels and serum TSH levels also did not show any statistical difference.

Table 5

Table showing Severity of depression in cases

Depression severity	Cases	
	No	%
Mild	2	8
Moderate	13	52
Severe	5	20
Severe with somatic syndrome	5	20
Total	25	100

Table 5 shows the severity of depression based on Hamilton rating scale for depression. Based on HAM-D scoring two patients (8%) had mild depression, 13 patients (52%) had moderate depression. Among patients with severe depression, 5 patients were categorized as severe depression with somatic syndrome.

CHART – 11

DEPRESSION SEVERITY IN MDD CASES

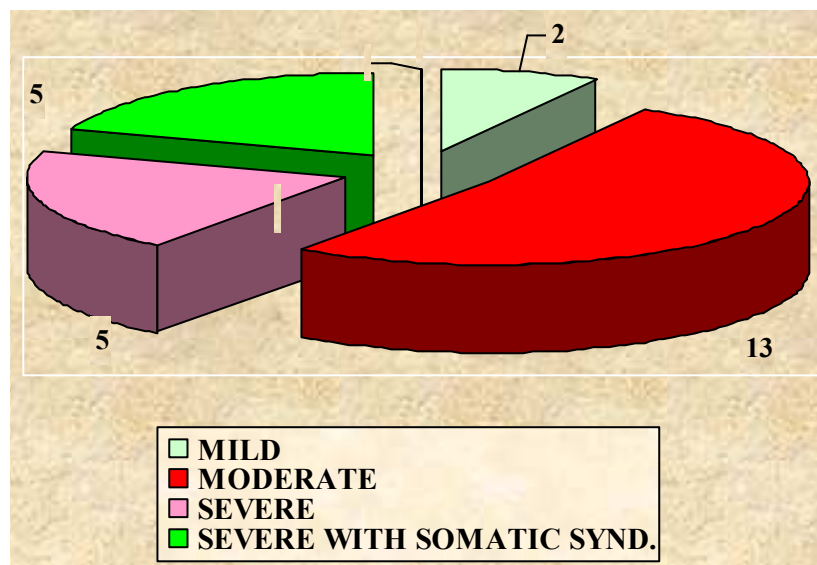


Table 6

Table showing relationship between socio Demographic variables and severity of depression

Sl. No	Variable	Severity of Depression								P value
		Mild		Moderate		Severe		Severe with S.S		
		No.	%	No.	%	No.	%	No.	%	
1	SEX									0.3012
	Male	0	0	2	40	2	40	1	20	
	Female	2	10	11	55	3	15	4	20	
2	MARITAL STATUS									0.6543
	Married	2	9.1	11	50	5	22.7	4	18.2	
	Unmarried	0	0	2	66.7	0	0	1	3.3	
3	SES									0.0182*
	Lower Middle	1	6.7	11	73.3	2	13.3	1	6.7	
	Upper Middle	1	10	2	20	3	30	4	40	
4	RESIDENCE									0.0533
	Rural	2	12.5	10	52.5	2	12.5	2	12.5	
	Urban	0	0	3	33.3	3	33.3	3	33.3	

[P < 0.05 *, P < 0.001**]

Table 6 shows the relationship between socio demographic variables and severity of depression. Depression severity and age of patients did not have any significant relationship. It shows that among five males with depression two belong to moderate and three belong to severe category. Among twenty females, two had mild, eleven had moderate and seven had severe depression, but the difference was not significant. Among depressive twenty two were married and three were unmarried and majority of married (44%) had moderate depression, nine patients (36 %) had severe depression. Severity of depression was not affected by the marital status of patients.

Regarding socio economic status fifteen patients 60% belong to low socio economic status and ten patients belong to middle socio economic status. Among patients with low socio economic status eleven patients (73.3%) had moderate depression and three patients (20%) had severe depression. Among middle socio economic status two patients (20%) had moderate depression and seven patients had (70%) had severe depression. The difference is statistically significant. No difference was noted in comparison between residential status and severity of depression.

CHART – 12

SOCIAL CLASS AND DEPRESSION SEVERITY

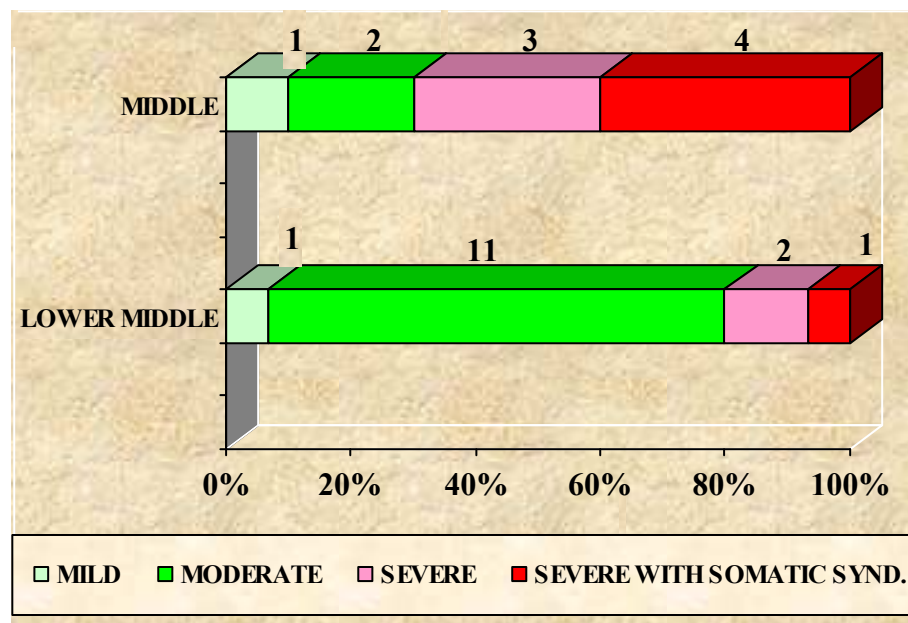


Table 7
Table showing Severity of depression and thyroid hormone values

S.No.	Variable	Thyroid hormone values					
1.	Severity of depression	T3 (ng/dl)		T4 (µg/dl)		TSH(mIU/ml)	
		Mean	SD	Mean	SD	Mean	SD
	Mild	83.5	4.9	7.55	0.64	0.74	0.12
	Moderate	103.5	16	9.68	1.64	2.2	1.81
	Severe	109.2	15.5	10.27	1.36	2.73	1.25
	Severe with somatic syndrome	115.2	9.5	10.7	1.83	3.02	4.33
	'p' value	0.0234*		0.0301*		0.2317	

[P < 0.05 *, P < 0.001**]

Table 7 shows the relationship between severity of depression and thyroid function values. The mean T3 level in mild depression is 83.5 and increases as the severity of depression increases with mean T3 in patients with severe depression with somatic syndrome was 115.2. As severity of depression increases mean T3 value also increases which was statistically significant. The same trend was noted in relation to serum T4 level with significantly high T4 levels in severe depression compared to mild or moderate depression. On comparison of TSH level, even though TSH values vary with severity of depression, the relationship was not statistically significant.

Table 8
Table showing Depression severity and PSLE score

Depression severity	PSLE Score		P value
	Mean	SD	0.0408 *
Mild	193.5	26.2	
Moderate	97.9	40.5	
Severe	163	68.8	
Severe with somatic syndrome	100.2	59.2	

[P < 0.05 *, P < 0.001**]

Table 8 shows the relationship between the severity of depression and presumptive stressful life event score. On comparison of life event scoring and severity of depression, mean score for mild and severe depression was significantly higher than moderate and severe depression with somatic syndrome.

Table :9

Table showing Socio demographic characteristics and thyroid profile

Characteristics	Thyroid Profile					
	T3		T4		TSH	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
AGE						
Upto 25	107.7	11.4	9.8	2.18	3.43	3.92
26-30	109.1	13.6	9.99	1.44	2.09	1.65
31-35	101.5	23.9	9.63	2.59	0.98	1.13
36-40	100.7	28.5	8.93	1.19	1.5	0.01
41-45	103.4	12.4	10.36	1.22	3.04	2.26
‘p’ value	0.736		0.8083		0.2844	
SEX						
Male	103	12.1	9.29	2.06	4.4	3.57
Female	106	16.8	9.97	1.63	1.84	1.66
‘p’ value	0.5398		0.4751		0.0351 *	
MARITAL STATUS						
Married	106	16.4	10.03	1.62	1.91	1.63
Unmarried	101	11.5	8.4	1.87	5.62	4.31
‘p’ value	0.476		0.1429		0.0365 *	
RESIDENCE						
Rural	107.4	15.1	9.87	1.7	2.6	2.74
Urban	101.9	17.2	9.77	1.8	1.92	1.31
SOCIAL CLASS						
Lower middle	104.4	18.2	10.17	1.72	1.79	1077
Upper Middle	106.9	12.0	9.33	1.61	3.2	2.86
‘p’ value	0.9114		0.2218		0.1341	

P < 0.05 * P < 0.001**

Table 9 : It shows the relationship between sociodemographic characteristics and thyroid profile. It shows no significant relation existing between age, residence and social class in relation to serumT3,T4 and TSH levels. On comparison of sex and serum TSH levels there is a significantly high TSH in men compared to women but no relationship seen between serum T3, serum T4 levels and sex.

Since the elevation of TSH level is within normal limits, the results do not reflect underlying subclinical hypothyroidism between sex.

On comparison of marital status and serum TSH levels there is a significantly high serum TSH in married person, but no correlation seen between T3,T4 and marital status.

DISCUSSION

The aim of the study is to assess the thyroid dysfunction in depression by assessment of basal thyroid hormone level.

The present study included only drug-naive patients having first episode of depressive illness. This way, the nonspecific effects of chronicity of illness and pharmacological agents on thyroid functions were taken care of. In our study we found that depression was more common in women, people from rural background and in younger individuals.

The most significant finding of our study was elevated levels of total thyroxin (T4) in the depressive patients in the acute phase of illness as compared to healthy controls. This is in agreement with most of the earlier studies (Whybrow et al.,1972; Takahashi et al.,1974; Kirkegaard and Faber,1981; Muller and Boning, 1988).V K Chopra .,et al 2001.

Bauer and Whybrow (1988) proposed that elevated total thyroxin (T4) during acute depression is a compensatory phenomenon so as to help in increasing the catecholamine neurotransmission for the alleviation of depressive affect. According to Jackson et al.,1999 most patients with depression although generally viewed as chemically euthyroid, have alterations in their thyroid function which includes slight elevation in their

serum thyroxine level. He postulated that hypercortisolism of depression leads to elevated T4 in some depressives.

According to Joffe.,et al 1990 the most consistent finding in acute depression was elevated total thyroxin T4 or free thyroxin Ft4 within the euthyroid range.

Joffe.,et al. (1984) and Joffe and Levitt (1990) proposed that relative increase in total thyroxin (T4) during acute depression is not compensatory, but is pathological indicating a relative state of hyperthyroidism and a substantial decrease in thyroxin level is required for recovery. Moreover significant decrease in T4level occurs with response to various treatments, including antidepressant, (Joffe RT & Levitt AJ.,et al 1993) (Bauer MS & Whybrow PC et al.,1988) (Kirkegaard C & Faber J et al.,1981), electroconvulsive therapy (Kirkegaard C & Faber J et al.,1986), and cognitive behaviour therapy (Joffe RT & Singer W.,et al 1996)

In our study, the levels of thyroxin (T4) were not preformed after the recovery and this remains one of its limitations.

Most of the studies of major depressive disorder have found an relative increase (ie. Within the normal range) in iodothyronine (most notably hyprethyroxinemia ie. FT4 or total T4). Neurobiologically this thyroid alterations has been proposed to represent a compensatory

mechanism to a pathological process that is depression or the primary pathology itself.

In our study we did not find any difference with respect to thyroid stimulating hormone (TSH) levels between the depressives and the control groups, although TSH values increased with the severity of the depression it was not statistically significant. This finding is similar to most of the previous studies (Takahashi et al., 1973; Linnola et al., 1979; Gold et al., 1981; Loosen & Prange 1982).

Cleare., et al 1996 found a positive correlation between depressive scores and the increase in TSH levels. A probable hypothesis for the increase in TSH in depression may be due to reduction in somatostatin as found by (Rubinow DR., et al 1983 & Bissette G., et al 1986), which normally inhibits the release of TSH from the hypophysis.

A study by Saxena J., et al 2000, found mildly depressed patients had significantly lower TSH and severely depressed patients had higher TSH suggesting the direct relationship of severity of depression and the TSH levels.

Regarding T3, we did not find any difference with respect to mean value of total triiodothyronine (T3) between depressives and controls.

The literature regarding total triiodothyronine (T3) during acute depression is less consistent. Takahashi et al. (1974) found marginally elevated T3 during acute depression whereas most of the other studies reported either normal or decreased total T3 during acute depression (Kirkegaard and Faber, 1981;

Kjellman et al., 1983; Sternback et al., 1985; Joffe et al., 1985; Orsulak et al., 1985; Baumgartner et al., 1988). Muller and Boning (1988) found elevated thyroxin (T4) and decreased triiodothyronine (T3) during acute depression and concluded that this finding may indicate that there is some defect in the conversion of thyroxin (T4) to triiodothyronine (T3). According to Nemeroff et al. 1989 noted defect in brain deiodinase can be a pathogenic factor in depression, which prevents conversion of T4 into active T3 in brain raising the possibility of central or brain hypothyroidism in the context of systemic euthyroidism.

Regarding the relationship between severity of depression and thyroid dysfunction in our study we found that the mean T3&T4 levels significantly increased as the severity of the depression increased. Even though the TSH levels also increased with the severity of the depression it was not statistically significant.

Joffe et al. (1992) did not find any difference between patients with melancholic and non-melancholic depression with respect to total thyroxin (T4), total triiodothyronine (T3) and thyroid stimulating hormone (TSH). In a study by Chopra VK et al, 2001 he did not find any difference with respect to any of the thyroid parameters between the depressive patients with and without the presence of somatic syndrome.

Fountaulakis., et al 2004 in his study he concluded that no significant differences can be traced concerning the thyroid function between clinical subtypes of depression nor any correlation between specific clinical symptoms and thyroid indices.

Apart from subtle changes in the thyroid functions, many studies have found overt thyroid abnormalities in a minority of depressive patients (Goldetal.,1981; Diaz-Cabaletal.,1986; Joffe et al.,1992).

We found a total of a 2 (8%) patients have grade II (Gold et al.,1981) subclinical hypothyroidism as suggested by elevated the TSH level and 2 patient (8%) having frank hyperthyroidism as suggested by elevated T4 level above normal values. According to Haggerty Jr .,et al 1993 the life time frequency of depression was significantly higher(56%) in subjects with

subclinical hypothyroidism than who did not (20%), suggesting that subclinical hypothyroidism may lower the threshold for depression. According to (Woodbury 1918: Brown-lie et al 2000) that in patients with hyperthyroidism depression can be prominent and found with symptoms of agitation rather than retardation. Kathol et al (1986) found that almost one – third of 29 consecutive patients seen in an endocrine clinic met criteria for major depression.

Considering the impact of stressful life events within one year of the onset of depression we found that depressives had significantly more life events than controls suggesting that stressful life events within one year significantly increase the onset of depression. This finding is similar to the previous studies (Grover et al.,2010). Several studies (Paykel et al., 1969:Cadoret 1972, Bidzinksa 1984) have documented that life events are very well associated with the onset of depressive disorders. Indian workers (Prakash.,et al1980,Chatterjee .,et al 1981)have found that depressives experience numerically more life events .In study by Suresh Kumar PN., et al although life events were significantly more in depressives, however there was no relationship between the severity of life events and the magnitude of illness in depressives. A Study by Niruj Agrawal & H.P.Jhingan 2002 reported that severity of depression was not found to be associated with

significantly higher life events, which showed that life event are associated with the occurrence of depression and not its severity.

This is consistent with our study where we found that even though depressives had significantly more life events it had no relationship with the severity of depression.

In the conclusion, we would like to emphasize that this study supports the view that there are subtle but significant abnormalities in the basal level of thyroid hormones in acute depressive illness. There is a need to continue the research efforts in this field to further clarify the aetiological significance of altered thyroid functioning in depressive illness.

Based on our finding it has been found that depression is common in younger age, women and those who are from rural background. On comparison of sociodemographic matched controls it has been found that T4 values was significantly higher in depressives compared to controls, but similar trend was not found with respect to T3&TSH levels. There has been a significantly higher occurrence of stressful life event and stressful life event scoring in depressive patients in the preceeding one year before the onset of illness. No significant correlation has been noticed between stressful life events and thyroid hormone values.

Majority of the sample were classified as having moderate and one fifth each as severe depression with somatic syndrome and severe depression without somatic syndrome. No significant relationship was observed on comparison of sociodemographic variable with relation to severity of depression except socioeconomic status. Severity of depression has been significantly related to serum T3&T4 levels, but not with TSH levels. No significant relationship between severity of depression and life event scoring. On comparison of sociodemographic profile and thyroid hormone level, there has been a significantly higher TSH level were found in men and those who are unmarried. The higher TSH level was within normal limits and hence in our study no significant difference noted between sex in relation to possible subclinical hypothyroidism.

CONCLUSION

Based on the detail analysis of depressives and controls the following conclusions are made:

1. Serum T4 level is significantly higher in depressives than controls.
2. Serum TSH level did not show significant difference between the depressives and controls.
3. Serum T3 & T4 level has been significantly rising with the severity of the depression.
4. Subclinical hypothyroidism did not show significant relation with sex.
5. Stressful life events has been significantly higher in the preceding one year to onset of depression but did not consistently increase with the severity of depression.

Future studies can be aimed at doing basal thyroid functions in all dimensions of depression including psychotic, bipolar and

puerperal depression, which will enlighten the possible thyroid dysfunction in patients with depressive disorder.

Further follow up studies will help in understanding the possible association of thyroid abnormalities in depressive disorder, their possible relationship with prognosis, treatment implications and treatment resistant depression.

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PRESUMPTIVE STRESSFUL LIFE - EVENTS SCALE

Name	Age	Sex
1. Going on a pleasure trip or pilgrimage(20)		0
2. Wife begins or stops work (25)		0
3. Change in eating habits(27)		0
4. Change in Social Activities(28)		0
5. Reduction in number of family function(29)		0
6. Gain of new family member(30)		0
7. Birth of Daughter(30)		0
8. Change in Sleeping habits (33)		0
9. Change in working conditions or transfer(33)		0
10. Retirement(35)		0
11. Begin or end schooling(36)		0
12. Outstanding personal achievement(37)		0
13. Change or expansion of business(37)		0
14. Change in residence(39)		0
15. Unfulfilled commitments(40)		0
16. Trouble with neighbour(40)		0
17. Getting married or engaged(43)		0
18. Appearing for examinations or interview(43)		0
19. Failure in examination(43)		0
20. Death of pet(44)		0
21. Major purchase or construction of house(46)		0
22. Breakup with friend(47)		0
23. Family conflict(47)		0
24. Minor violation of Law(48)		0

25. Marriage of daughter or dependent sister(49)	()
26. Large Loan(49)	()
27. Lack of son(51)	()
28. Self or family member unemployed (51)	()
29. Sexual problems(51)	()
30. Conflict over dowry (self or spouse) (51)	()
31. Pregnancy of wife (wanted or unwanted) (54)	()
32. Prophecy of astrologer or palmist etc.(59)	()
33. Trouble at work with colleague, superiors or subordinates(52)	()
34. Illness of family member (52)	()
35. Financial loss or problems(54)	()
36. Son or daughter leaving home(55)	()
37. Major personal illness or injury (56)	()
38. Broken engagement or love affair(57)	()
39. Conflict with in-laws (other than dowry) (57)	()
40. Robbery or theft (59)	()
41. Excessive alcohol or drug use by family member(58)	()
42. Death of friend (60)	()
43. Property or crops damaged (61)	()
44. Marital Conflict (64)	()
45. Death of close family member(66)	()
46. Lack of child(67)	()
47. Determination in Jail of Self or close family member(78)	()
48. Suspension or dismissal from Job (76)	()
49. Marital Separation / divorce (77)	()
50. Extra marital relation of spouse (80)	()

51. Death of spouse (95) 0

Total number of life events present 0

Total Score - 0

Up to 40 No stress

41-200 Less / moderate stress

>200 Severe stress

**A STUDY OF BASAL THYROID FUNCTIONS IN DRUG NAIVE
FIRST EPISODE DEPRESSION**

SOCIODEMOGRAPHIC AND CLINICAL DATA:

NAME: **AGE:** **SEX: F/M**

ADDRESS:

EDUCATION: **ILLITRATE/upto10th/more than 10th**

RURAL/URBAN:

MARITAL STATUS:

OCCUPATION:

SOCIO ECONOMIC STATUS: **LOW/MIDDLE/UPPER**

INFORMANT:

SYMPTOMS:

HOPI:

PAST H/O:

Previous H/O Psychiatric illness:

Treatment History:

Systemic illness:

Family H/O:

H/O psychiatric illness:

Medical illness:

Personal H/O:

Menstrual History:

Substance Use:

Marital H/O:

Premorbid Personality:

G/E:

Vitals:

Anemia/jaundice/Goiter

Systemic Examination:

CVS:

RS:

P/A:

CNS:

MSE :

ICD10 (DCR) Diagnosis :

Blood and Urine Investigations :

Serum T3 level

T4 level

TSH level

HAMILTON DEPRESSION SCALE

1. Depressed mood

Sad, hopeless, helpless, worthless

0 = Absent

1 = Gloomy attitude, pessimism, hopelessness

2 = Occasional weeping

3 = Frequent weeping

4 = Patient reports highlight these feelings states in his/her spontaneous verbal and non-verbal communication.

2. Feelings of guilt

0 = Absent

1 = Self-reproach, feels he/she has let people down

2 = Ideas of guilt or rumination over past errors or sinful deeds

3 = Present illness is punishment

4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations. Delusions of guilt.

3. Suicide

0 = Absent

1 = Feels life is not worth living

2 = Wishes he/she were dead, or any thoughts of possible death to self

3 = Suicide, ideas or half-hearted attempt

4 = Attempts at suicide (any serious attempt rates 4)

4. Insomnia, early

0 = No difficulty falling asleep

1 = Complaints of occasional difficulty in falling asleep i.e. more than half-hour

2 = Complaints of nightly difficulty falling asleep

5. Insomnia, middle

0 = No difficulty

1 = Patient complains of being restless and disturbed during the night

2 = Walking during the night – any getting out of bed rates 2 (except voiding bladder)

6. Insomnia, late

0 = No difficulty

1 = Waking in the early hours of the morning but goes back to sleep

2 = Unable to fall asleep again if he/she gets out of bed

7. Work and activities

0 = No difficulty

1 = Thoughts and feelings of incapacity related to activities: work or hobbies

2 = Loss of interest in activity – hobbies or work – either directly reported by patient or indirectly seen in listlessness, in decisions and vacillation (feels he/she has to push self to work or activities)

3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities

4 = Stopped working because of present illness. In hospital rate 4 if patient engages in no activities except supervised ward chores

8.Retardation

**Slowness of thought and speech; impaired ability to concentrate;
decreased motor activity**

0 = Normal speech and thought

1 = Slight retardation at interview

2 = Obvious retardation at interview

3 = Interview difficult

4 = Interview impossible

9.Agitation

0 = None

1 = Fidgetiness

2 = Playing with hands, hair, obvious restlessness

3 = Moving about; can't sit still

**4 = Hand wringing, nail biting, hair pulling, biting of lips, patient is on
the run**

10.Anxiety, psychic

Demonstrated by:

0-No difficulty

1- subjective tension and irritability, loss of concentration

2- worrying about minor matters

3- apprehension

4- fears expressed without questioning

5- feelings of panic

6- feeling jumpy

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

4 = Incapacitating

11. Anxiety, somatic

Physiological concomitants of anxiety such as:

- **gastrointestinal: dry mouth, wind, indigestion, diarrhea, cramps, belching**
- **cardiovascular: palpations, headaches**
- **respiratory: hyperventilation, sighing**
- **urinary frequency**
- **sweating**
- **giddiness, blurred vision**
- **tinnitus**

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

4 = Incapacitating

12. Somatic symptoms: gastrointestinal

0 = None

1 = Loss of appetite but eating without encouragement

2 = Difficulty eating without urging. Requests or requires laxatives or medication for GI symptoms

13.Somatic symptoms: general

0 = None

1 = Heaviness in limbs, back or head; backaches, headaches, muscle aches, loss of energy, fatigability

2 = Any clear-cut symptom rates 2

14.General Symptoms

Symptoms such as: loss of libido, menstrual disturbances

0 = Absent

1 = Mild

2 = Severe

15.Hypochondriasis

0 = Not present

1 = Self-absorption (bodily)

2 = Preoccupation with health

3 = Strong conviction of some bodily illness

4 = Hypochondrial delusions

16.Loss of weight

0 = No weight loss

1 = Probable weight loss associated with present illness

2 = Definite (according to patient) weight loss

B Actual weight changes (weekly):

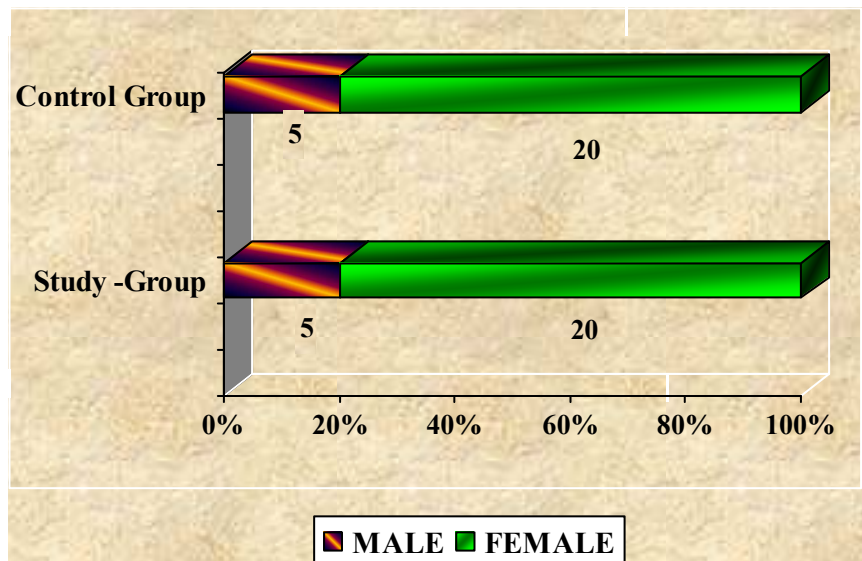
17. Insight

- 0 = Acknowledges being depressed and ill**
- 1 = Acknowledges illness but attributes cause to bad
food,
overwork, virus, need for rest, etc.**
- 2 = Denies being ill at all**

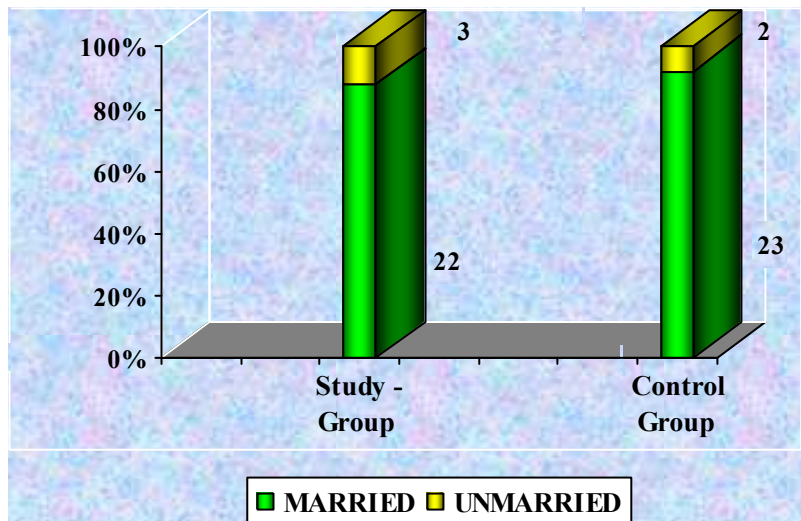
HAMD – SCORE INTERPRETATION

- 0 – 7 - None / minimal depression**
- 8 – 17 - Mild**
- 18 – 25 - Moderate**
- > 25 - Severe**

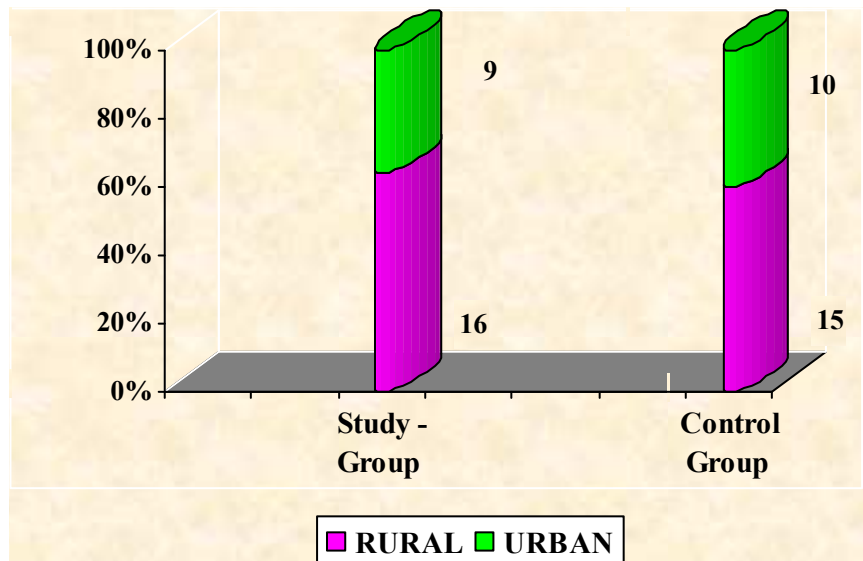
SEX DISTRIBUTION



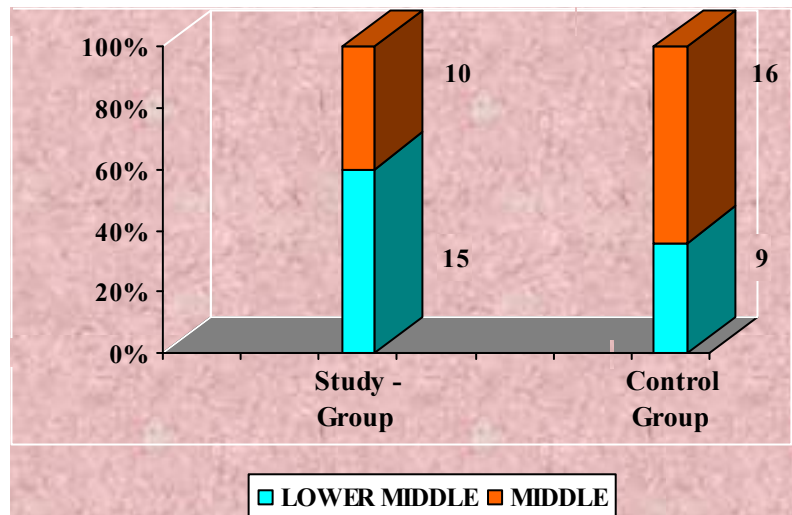
MARITAL STATUS DISTRIBUTION



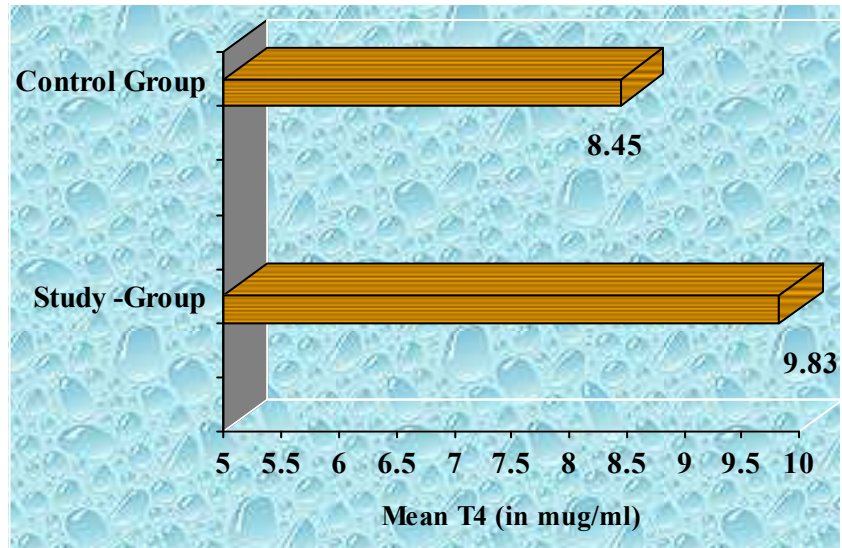
RESIDENCE DISTRIBUTION



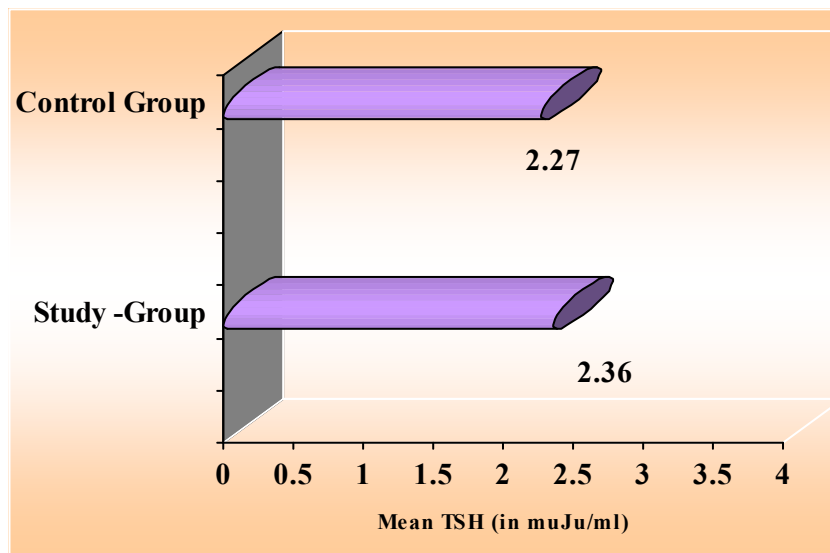
SOCIAL CLASS DISTRIBUTION



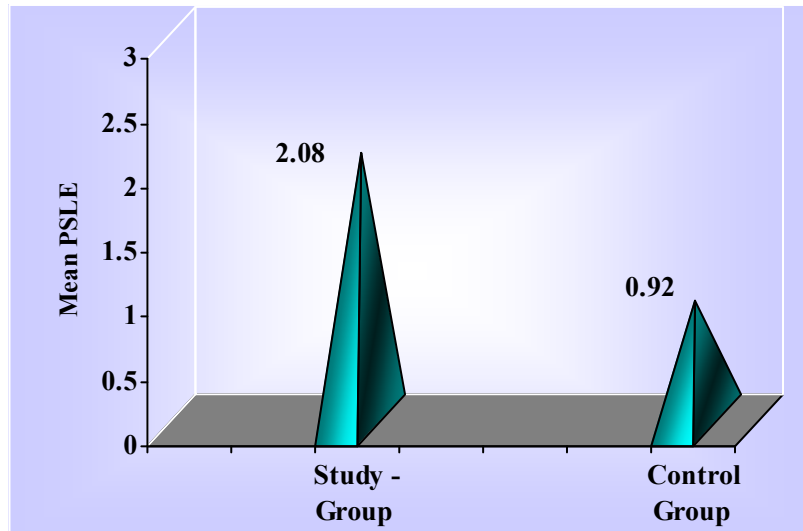
MEAN T4



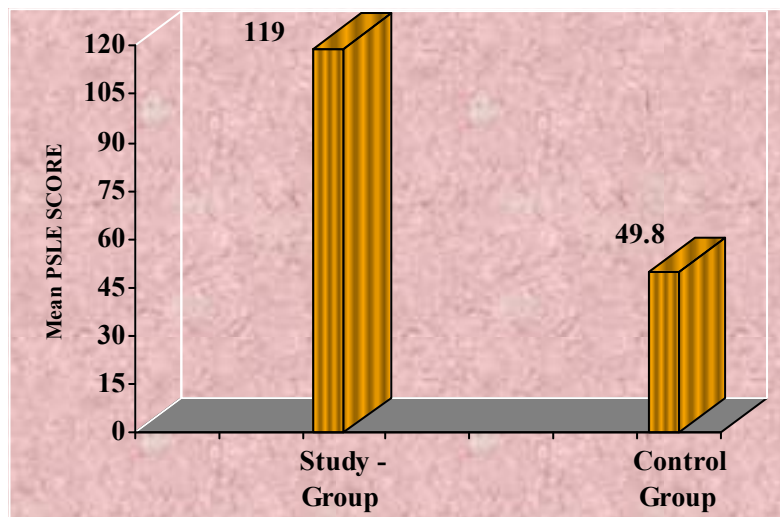
MEAN TSH



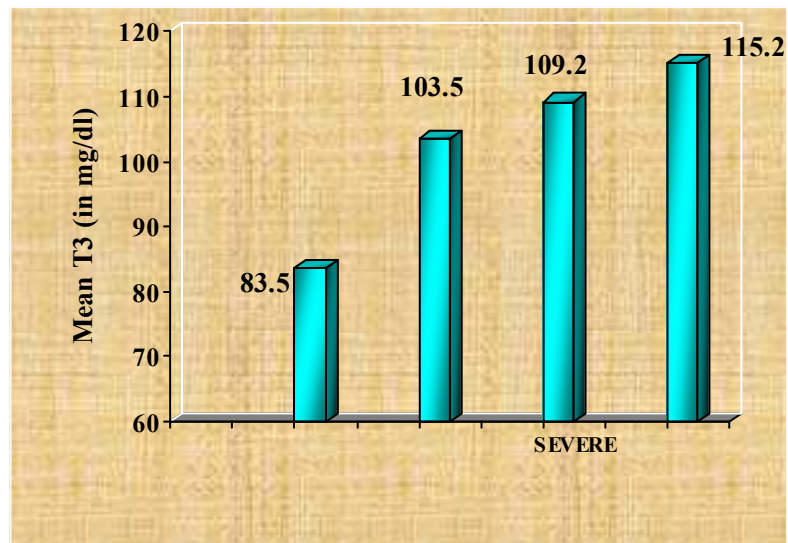
MEAN PSLE



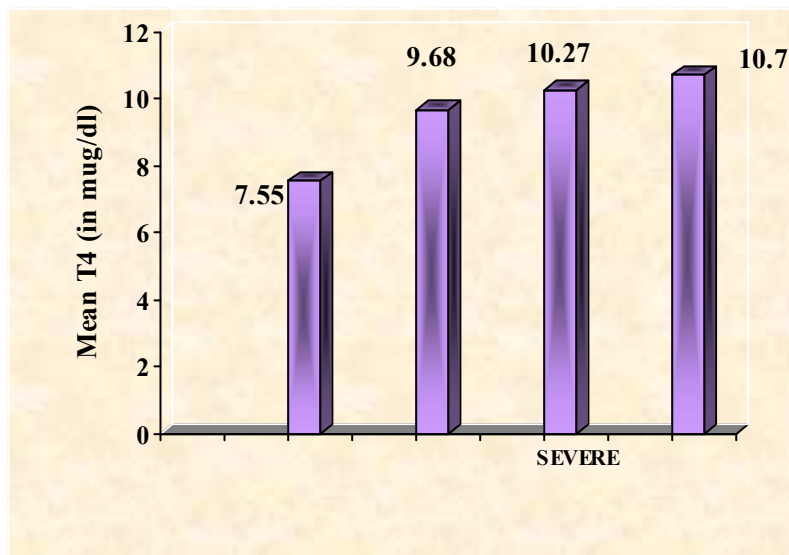
MEAN PSLE SCORE



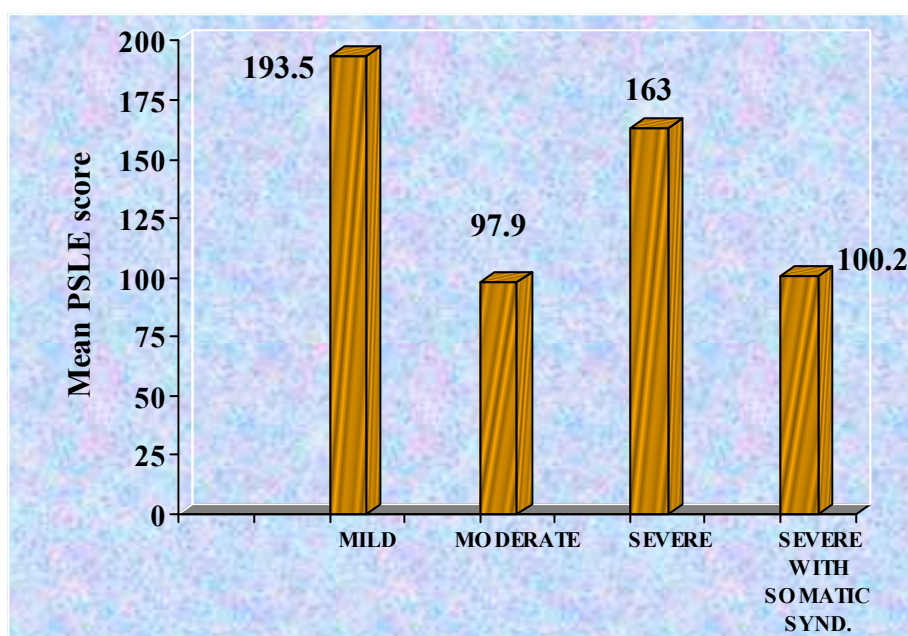
DEPRESSION SEVERITY & T3 VALUES IN MDD CASES



DEPRESSION SEVERITY & T4 VALUES IN MDD CASES



DEPRESSION SEVERITY & PSLE SCORE IN MDD CASES



MASTER CHART - CASES									
S.No.	Age	Sex	MARITAL STATUS	Depression severity	Social class	PSLE	T3 60-200 ng/dl	T4 4.5 - 12 g/dl	TSH 0.3 - 5.5 mIU/ml
1	42	F	MARRIED	Moderate	Lower middle	No.2 Total 101	90	9.00	6.50
2	25	F	MARRIED	Severe with somatic syndrome	upper middle	No.3 Total 201	114	11.90	1.02
3	30	F	MARRIED	Severe	upper middle	No.4 Total 247	107	8.70	2.87
4	30	F	MARRIED	Moderate	Lower middle	No.2 Total 113	118	10.30	0.85
5	29	F	MARRIED	Mild	upper middle	No.3 Total 175	87	8.00	0.65
6	30	F	MARRIED	Severe with somatic syndrome	upper middle	No.1 Total 67	118	10.30	0.85
7	33	F	MARRIED	Moderate	Lower middle	No.1 Total 67	82	10.20	0.47
8	33	F	MARRIED	Severe with somatic syndrome	Lower middle	No.2 Total 106	126	13.00	0.03
9	30	F	MARRIED	Moderate	Lower middle	No.2 Total 113	120	11.50	4.68
10	39	F	MARRIED	Moderate	Lower middle	No.3 Total 160	96	8.40	1.50
11	32	F	MARRIED	Mild	Lower middle	No.4 Total 212	80	7.10	0.82
12	38	F	MARRIED	Severe	Lower middle	No.2 Total 113	131	10.30	1.49
13	25	F	MARRIED	Moderate	Lower middle	No.1 Total 49	107	12.30	0.08
14	45	F	MARRIED	Moderate	Lower	No.1 Total 67	115	10.13	1.16

6	29	F	MARRIED	Lower middle	No.1 Total 52	87	8.80	0.97
7	29	F	MARRIED	Upper middle	No.2 total 121	121	9.40	1.51
8	26	F	MARRIED	Upper middle	No.2 total 134	92	9.50	1.44
9	31	F	MARRIED	Lower middle	No.1 Total 49	92	8.50	1.57
10	30	F	MARRIED	Upper middle	Nil	96	11.10	3.68
11	43	F	MARRIED	Lower middle	No.1 Total 52	93	8.00	4.34
12	40	F	MARRIED	Lower middle	No.1 Total 52	105	7.10	3.03
13	27	F	MARRIED	Upper middle	Nil	89	6.70	3.69
14	32	F	MARRIED	Upper middle	No.2 total 101	113	8.20	0.91
15	33	F	MARRIED	Lower middle	No.1 Total 52	107	8.60	3.57
16	25	F	UN MARRIED	Upper middle	No.1 Total 52	86	8.60	2.57
17	29	F	MARRIED	Upper middle	No.2 Total 116	93	9.20	0.87
18	32	F	MARRIED	Upper middle	No.1 Total 52	122	7.60	1.59
19	45	F	MARRIED	Upper middle	Nil	90	8.80	1.95
20	28	F	MARRIED	Upper middle	Nil	87	5.40	5.18
21	37	M	MARRIED	Upper middle	No.1 Total 54	141	9.80	2.21
22	25	M	UN MARRIED	Upper middle	Nil	113	8.20	1.57
23	35	M	MARRIED	Lower middle	Nil	131	9.60	2.39
24	31	M	MARRIED	Upper middle	No.1 Total 57	89	8.60	2.28
25	34	M	MARRIED	Lower middle	No.1 Total 52	116	8.80	1.48

ABSTRACT

Objective: To assess the basal thyroid functions in drug naive patients with first episode depression.

Methods: Sample of 50 , of whom 25 are newly diagnosed as depressive disorder according to ICD-10 DCR, who are drug naive and equal number of healthy, age and sex matched controls were included in this study. HAM-D scale was used to classify the degree of depression into mild, moderate and severe grades. The thyroid hormone levels (T3,T4 & TSH) were estimated. The PSLE scale was used to assess the impact of stressful life events on the onset and severity of depression. The data were analyzed using chi-square for categorical variables and student 't' test for numerical variables.

Results: Serum T4 level is significantly higher in depressives than controls. Serum T3 and T4 level has been significantly rising with the severity of depression. Stressful life events has been significantly higher in the preceding one year to onset of depression.

Conclusion: This study points towards a significant but subtle abnormalities in the thyroid functions in depressed patients. Thus inclusion of thyroid screening test among depressives may be helpful in assessing their possible relationship with prognosis, treatment implications and treatment resistant depression.

Keywords: First episode depression, drug naive patients, thyroid function tests.